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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/567,872

05/19/2006

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EXAMINER

SHEN, WU CHENG WINSTON

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/567,872	<b>Applicant(s)</b> FISHBEIN ET AL.	
	<b>Examiner</b> WU-CHENG Winston SHEN	<b>Art Unit</b> 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 05 January 2010.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,3,8-10,17-28 and 35-37 is/are pending in the application.
- 4a) Of the above claim(s) 17-28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3,8-10 and 35-37 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 08 February 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                     |                                                                   |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                    | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____                                                         | 6) <input type="checkbox"/> Other: _____                          |

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### **DETAILED ACTION**

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/05/2010 has been entered.

Claims 2, 4-7, 11-16, 29-34, and 38-40 are cancelled. Claims 1, 3, 8-10, 17-28, and 35-37 are pending. Claims 1 and 35 have been amended.

Claims 17-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 1, 3, 8-10, and 35-37 are currently under examination.

This application 10/567,872 is a 371 of PCT/US04/26509 filed on 08/13/2004, which claims benefit of 60/494,886 filed on 08/13/2003.

### ***Claim Rejection - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed on 01/05/2010.*

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Claim 35 has been amended to read as follows: The composition of claim 1, wherein the modified protein comprises a fragment of a CAR protein.

Claim 37 reads as follows: The composition of claim 35, wherein the receptor targeting ligand is selected from the group consisting of apolipoprotein E, transferrin, a vascular endothelial growth factor, a transforming growth factor-beta, a fibroblast growth factor, an RGD containing peptide, and folic acid.

Claim 37 is dependent from claim 35 and recites the limitation “the receptor targeting ligand” in “wherein the receptor targeting ligand is selected from the group consisting of apolipoprotein E, transferrin, a vascular endothelial growth factor, a transforming growth factor-beta, a fibroblast growth factor, an RGD containing peptide, and folic acid”. There is insufficient antecedent basis for this limitation in the claim.

### ***Claim Rejection - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 1, 3, 8-10, and 35-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Levy et al.** (U.S. 2003/0044408, publication date, 03/06/2003, filed on 06/14/2000; this reference is cited in the IDS filed by Applicant on 08/20/2008) in view of **Li** (US patent 6,524,572, issued date 02/25/2003, filed on 09/26/2000). Applicant's arguments filed 01/05/2010 have been fully considered and they are not persuasive. Previous rejection is

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***maintained*** for the reasons of record advanced on pages 5-10 of the office action mailed on 11/23/2009 and is reiterated below with revisions addressing claim amendments filed on 01/05/2010.

Amended claim 1 filed on 01/05/2010 reads as follows: A composition comprising a metal surface chemically coordinated to a surface modifier and a modified protein, wherein the modified protein comprises a CAR protein, or a fragment of a CAR protein, and wherein the modified protein is covalently bound to the surface modifier directly or via a linker.

Claim 3 further limits claim 1 by the limitation wherein the modified protein is covalently bound to the surface modifier through a thio residue and a linker.

Claim 8 further limits the metal surface being a surface of a medical device.

Claim 9 further limits claim 8 to medical device selected from the group consisting of a stent, a heart valve, a wire suture, a joint replacement, a urinary dilator, an orthopedic dilator, a catheter and an endotracheal tube.

Claim 10 further limits claim 8 to the medical device being at least one of an internal device and an external device.

Claim 35 further limits claim 1 by the limitation wherein the modified protein comprises a fragment of a CAR protein.

Claim 36 further limits claim 35 by the limitation wherein the fragment of the CAR protein is an extracellular domain of CAR or an immunoglobulin D1 domain of CAR.

Claim 37 further limits claim 35 by the limitation wherein the receptor targeting ligand is selected from the group consisting of apolipoprotein E, transferrin, a vascular endothelial growth factor, a transforming growth factor-beta, a fibroblast growth factor, an RGD containing peptide, and folic acid.

*Claim interpretations:* **(i)** The “receptor targeting ligand” recited in claim 37 is interpreted as part of the “modified protein” recited in claim 35, and **(ii)** The limitation “wherein the modified protein comprises a CAR protein, or a fragment of a CAR protein” recited in claim 1 encompasses the modified protein is a fusion protein. This interpretation is consistent with the word “comprising”, which allows the presence of non-specified sequences, and is consistent with the interpretation of claim 37 stated in **(i)**.

With regard to limitations of claims 1, 8, and 10, **Levy et al.** teaches a composition comprising a surface modifier and a metal support to which said surface modifier is chemically coordinated. Preferably, the surface modifier is an aminobisphosphonate. Levy et al. teaches that, still preferred, the surface modifier is a polyamine, and in another aspect of the invention, the composition further comprises a biologically active molecule. Levy et al. teaches that in another preferred embodiment, the biologically active molecule is an antibody which specifically binds a nucleic acid; and also preferred the nucleic acid comprises a vector system. Levy et al. teaches that in yet another aspect of the invention, the biologically active molecule is preferably one component of an affinity pairing system, and still preferred, the biologically active molecule is avidin or biotin; IgG or protein A; or transferrin or its receptor (See paragraph [0008], Levy et al., 2003/0044408, 2003). Levy teaches that a therapeutic delivery system efficiently introduces biologically active molecules to mammalian cells without the use of synthetic polymers or biopolymer coatings. Levy teaches that surface modification of a metal support, such as stainless steel and titanium medical devices, a stainless steel stent, results in a single molecular layer that can fasten various molecules, thereby minimizing any cellular inflammatory response while enhancing biocompatibility (See abstract, and paragraph [0003] and [0010] Levy et al., 2003). Levy et al. teaches that the paired component which is most suitable for attachment to the surface-modified metal would be immobilized. The component is covalently cross-linked to a monomeric or polymeric surface modifier, which, in turn, provides chemical moieties that bind to the metal surface (See abstract, and paragraph [0026] and [0037], Levy et al., 2003).

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With regard to the limitation “wherein the modified protein is covalently bound to the surface modifier through thiol residue and a linker” recited in claim 3, Levy teaches that in Fig. 2 depicts a reaction scheme for modifying surfaces of metal supports via amino group containing bisphosphonates. During an activation step, the N-succinimidyl ester group in SPDP (N-succinimidyl-3-(2-pyridyl- dithio)-propionate) reacts with the amino group of a chemisorbed polyamino-bisphosphonic acid, to activate a steel surface with a pyridyldithio group, and during a modification step, a thiol modified antibody is chemically linked to the metal (See paragraph [0013], US 2003/0044408. Levy et al, 2003).

With regard to the limitation of medical devices recited in claim 9 and the limitation of internal device and external device recited in claim 10, Levy et al. teaches that medical devices may include non-orthopedic devices, temporary placements and permanent implants, such as tracheostomy devices, intraurethral and other genitourinary implants, stylets, dilators, stents, vascular clips and filters, pacemakers [which reads on internal device], wire guides and access ports of subcutaneously implanted vascular catheters [which reads on external device]. (See paragraph [0036], US 2003/0044408. Levy et al, 2003).

Related to the limitation “wherein the modified protein comprises a fusion protein, or a CAR protein, or a fragment of a CAR protein” recited in claim 1, the limitation “wherein the modified protein is comprises fragment of a CAR protein” recited in claim 35, the extracellular domain of CAR or an immunoglobulin D1 domain of CAR recited in claim 36, and the receptor targeting ligand recited in claim 37, Levy et al. teaches the composition comprises a biologically active molecule. Levy et al. teaches that the biologically active molecule is preferably one component of an affinity pairing system, and still preferred, the biologically active molecule is

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avidin or biotin; IgG or protein A; or transferrin or its receptor (See paragraph [0008], US 2003/0044408. Levy et al, 2003).

Levy et al. does not explicitly teach the limitation “wherein the modified protein comprises a CAR protein, or a fragment of a CAR protein” recited in claim 1, the limitation “wherein the modified protein comprises fragment of a CAR protein and a receptor targeting ligand” recited in claim 35, the fragment/domain of the CAR protein recited in claim 36, and the receptor targeting ligand recited in claim 37.

Li teaches recombinant virus with a bispecific fusion protein ligand in coupling with an antibody to cell for gene therapy, and the fusion protein comprises extracellular domain of CAR/Hinge/protein A ligand, and Li develops a strategy using adenovirus as an example to demonstrate the strategy of using the fusion protein to re-direct viral tropism (See title, abstract and Figure 1, Li). Li teaches that any extracellular domain of a viral receptor that is a membrane protein or membrane peptide can be used to replace extracellular domain of CAR and can be inserted as a part of the fusion protein ligand for targeting (See lines 20-24, column 8, Li). Li teaches that Arg-Gly-Asp (RGD) motif of viral pentose protein binds to integrins of cell membrane and this binding activates virus internalization via receptor-mediated endocytosis (lines 53-58, column 1, Li)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Levy et al. regarding a composition comprising a surface modifier and a metal support to which said surface modifier is chemically coordinated, and the composition further comprises a biologically active molecule, the biologically active molecule being an antibody, and also preferred, the biologically active



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molecule being preferably one component of an affinity pairing system, and still preferred, the biologically active molecule is avidin or biotin; IgG or protein A; or transferrin or its receptor, with the teaching of Li regarding fusion protein comprises extracellular domain of CAR/receptor targeting ligand, to arrive at the claimed invention of claims 1, 3, 8-10, and 35-37.

One having ordinary skill in the art would have been motivated to combine the teachings of Levy et al. and Li et al. because the fusion protein taught by Li can target specifically the receptor of interest present on cell membrane in the context of using viral vector to deliver therapeutic agent via the metal surface of a medical device, for instance, a stent taught by Levy et al.

There would have been a reasonable expectation of success given (i) successful demonstration of a composition comprising a surface modifier and a metal support to which said surface modifier is chemically coordinated, and the composition further comprises a biologically active molecule, and virus tethering stainless steel and in vivo cell transduction (See Example 5 of Levy et al.), by the teachings of Levy et al., and (ii) successful construction of the fusion protein comprises extracellular domain of CAR/receptor targeting ligand, by the teachings of Li.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

### ***Applicant's arguments***

Applicants state that Applicants disagree that the claims are *prima facie* obvious over Levy in view of Li, because the proposed combination of Levy and Li does not supply all of the features of the amended claims. The claims recite a composition comprising a CAR protein or a fragment of a CAR protein. Neither Levy nor Li teach or suggest a CAR protein or fragments

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thereof. Applicants state that the cited references, whether considered alone or in the combination proposed by the Office Action, do not provide all of the claimed features the rejection fails to establish prima facie obviousness of the claimed invention.

***Response to Applicant's arguments***

As stated in the maintained rejection, **Li** teaches recombinant virus with a bispecific fusion protein ligand in coupling with an antibody to cell for gene therapy, and the fusion protein comprises extracellular domain of CAR/Hinge/protein A ligand, and Li develops a strategy using adenovirus as an example to demonstrate the strategy of using the fusion protein to re-direct viral tropism (See title, abstract and Figure 1, Li). Li teaches that any extracellular domain of a viral receptor that is a membrane protein or membrane peptide can be used to replace extracellular domain of CAR and can be inserted as a part of the fusion protein ligand for targeting (See lines 20-24, column 8, Li). Li teaches that Arg-Gly-Asp (RGD) motif of viral pentose protein binds to integrins of cell membrane and this binding activates virus internalization via receptor-mediated endocytosis (lines 53-58, column 1, Li).

Applicant's attention is also directed to the claim interpretations, which indicates that **(i)** the "receptor targeting ligand" recited in claim 37 is interpreted as part of the "modified protein" recited in claim 35, and **(ii)** the limitation "wherein the modified protein comprises a CAR protein, or a fragment of a CAR protein" recited in claim 1 encompasses the modified protein is a fusion protein.

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3. Previous rejection of claim 34 under 35 U.S.C. 103(a) as being unpatentable over **Levy et al.** (U.S. 2003/0044408, publication date, 03/06/2003, filed on 06/14/2000; this reference is cited in the IDS filed by Applicant on 08/20/2008) in view of **Li** (US patent 6,524,572, issued date 02/25/2003, filed on 09/26/2000), as applied to claims 1, 3, 8-10, and 35-37 above, and further in view of **Xu et al.** (US patent 7,001,745, issued date 02/21/2006, filed on 09/30/1999) is *moot* because the claim has been cancelled.

### ***Conclusion***

4. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

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may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/

Patent Examiner

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